Regulatory Expectations For Process Validation

WCBP Training Session
January 10, 2004

Chris Joneckis, Ph.D.
Senior Advisor For CMC Issues
Center For Biologics Evaluation And Research

U.S. Department of Health and Human Services
Food and Drug Administratio

Presentation Overview

- Background/ History
- Goals/ Principles
- Lifecycle Approach
  - Expectations, Issues
- Process Analytical Technologies and Validation
- Summary

Process Validation Background

- Promulgated in 1978 GMP rule
  - Essential component of demonstrating control of the manufacturing process
- Guideline on General Principles of Process Validation, [May, 1987]
- "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics." [FDA Guideline General Principles of Process Validation, May 1987 *emphasis added*]

Why Validation?

"Quality By Design"

- Reasons
  - Quality safety and effectiveness must be designed and built into the product
  - Quality cannot be inspected or tested into the finished product
  - Each step must be controlled to maximize the probability that the finished product meets all specifications
- Benefits
  - Provide assurance for consistent manufacture of a quality product
  - Public health
  - Regulatory
  - Economic

Principles

- Controlled Process
- Demonstration of consistency/ reproducibility
- Process operating limits - not edge of failure
  - "… process when operated according to procedures will consistently yield product with the specified quality attribute." [FDA Guideline General Principles of Process Validation, May 1987]Principles
- "Robustness" "Worst Case" "Most appropriate challenge"
  - "A set of conditions encompassing upper and lower processing limits and circumstances, including those with the standard operating procedure, which pose the greatest chance of process failure when compared to ideal conditions" [FDA Guideline General Principles of Process Validation, May 1987]

Foundation

- Process and product understanding "knowledge"
  - Well defined and designed product and manufacturing process
- Accurate measure of variability
  - Consider all sources of variability
- Supported by documentation, data

Principles

- Generally Prospective
  - **Validation conducted and completed prior to the distribution of either a new product, or a product made under a revised manufacturing process, where the revisions may affect the products characteristics [General Principles of Process Validation, 1987]**
- Concurrent validation
  - Orphan products
  - Elements (e.g., column resin life)
  - Heightened testing

Process Validation - History

- Proposed revision to cGMP regulations [May, 1996; Fed.Reg., Vol. 61, No. 87]
  - 21 CFR 210.3 (24) - validation definition
  - 21 CFR 211.220 - validation, protocols, design, QA
- ICH Q7A GMP for API [August, 2001]

Considerations

- CGMP Initiative For the 21st Century
  - Desired State of Manufacturing
  - Facilitate Continuous Improvement and Innovation
  - Risk Assessment and Mitigation
  - Process Analytical Technologies
  - Discussion of Process Validation
- Variety of established and developing products
  - Varying complexity
  - Various degrees of process understanding and control
    - **Chemical/ synthetic pharmaceuticals**
    - **Biological and biotechnological products**

Considerations

- Differing approaches to process validation
  - Empirical approach – based upon available information/ manufacturing experience
  - Three conformance batches is sufficient
  - Process approach - reliance on scientific and engineering principles
- Compliance Policy Guide for API – Process Validation Requirements for Drug Products and API's Subject to Pre-Market Approval [March 2004]
  - Not applicable to biotechnology and biological products
  - Provides some clarifications to validation

Common Approach for Biotechnology and Biological Product Validation

- Common practice has developed in approaches to process validation for biotechnological and biological products
- Process validation is viewed as a process that occurs throughout the lifecycle of a product
  - Through a series of activities, knowledge accumulates resulting in increasing assurance that a product meeting predetermined quality attributes will be manufactured.
  - Confidence building
- Integrated activity requiring information from multiple areas

Process Validation Program

ource/starting material
haracterization

aw materials
ualification

tudies for clearance of
ruses/ impurities-
ontrol of production
cale

accine/toxin
nactivation on
roduction scale

Development Studies

Equipment
IQ, OQ, PQ

Conformance Lots – "validation study"

Materials qualification

Analytical Methods
and Assay Qualification

Product
Characterization

Accumulated
manufacturing
experience

"Validated Process"

Change Contr
Monitoring/Tre
(Statistical Pro
Control PC)

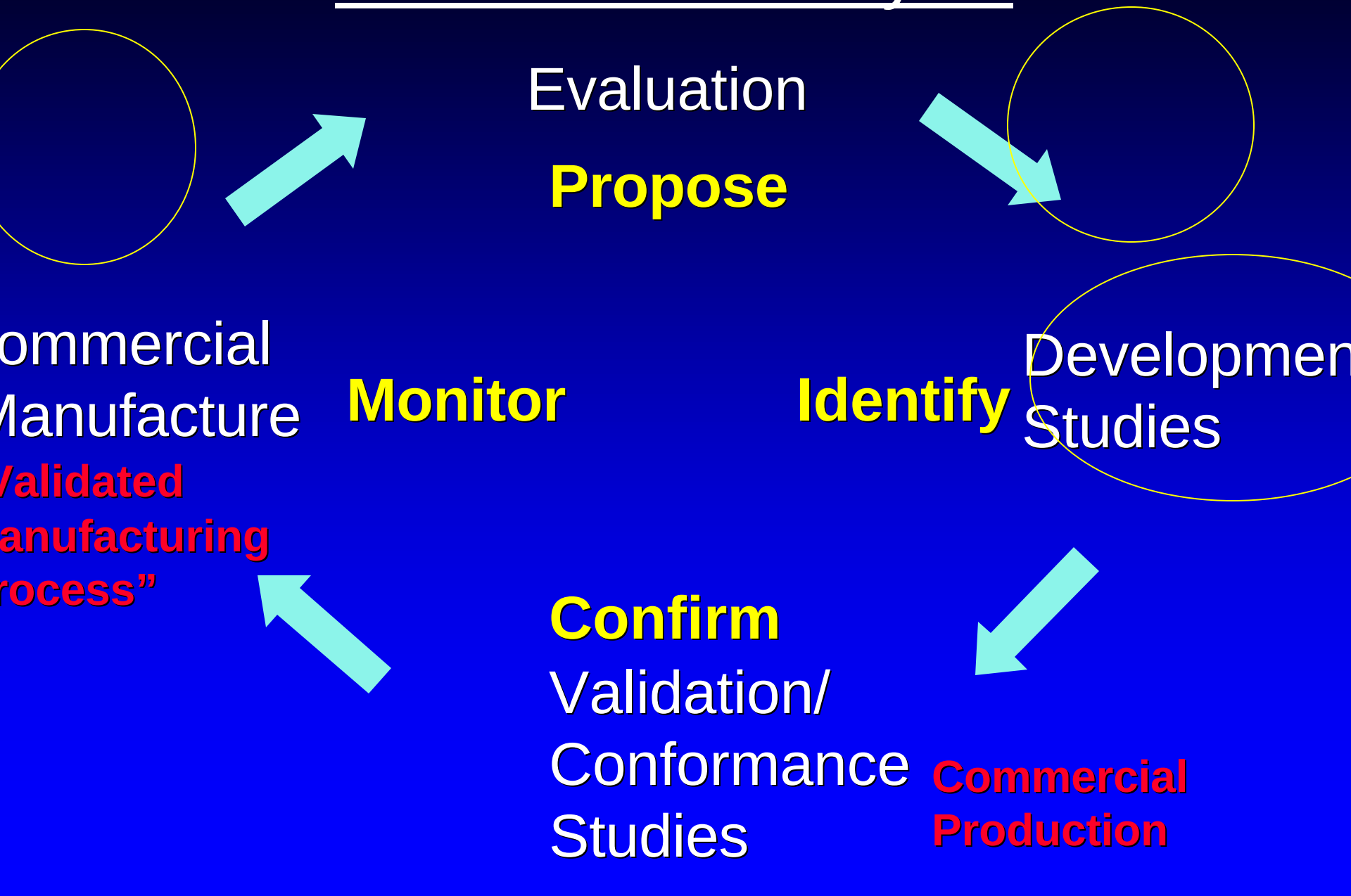
Discovery
Pre-clinical

Clinical (IND)

BLA

Post-Approv

Validation Life Cycle



Evaluation (Propose)

- GOAL: Propose process unit operations and process variables (operating parameters) that need to be validated
- Modular evaluation - evaluate process by unit operations
- Risk Assessment
  - Based upon experience, knowledge, & understanding,
  - Requires understanding of process and product
  - (intermediate, drug substance and drug product)
- Select subset of operating parameters to test in “representative” models
  - Critical and *questionable* variables

Evaluation (Propose)

- Considerations
  - Risk Assessment
    - Selection of Approach - Many approaches – (e.g., FMEA, HACCP elements)
    - ICH Q9 Quality Risk Assessment – Toolbox
    - Subjective elements
      - Judgment error
      - Not include questionable variable that turn out to be critical
- Definition of Critical

Development Studies (Identify)

- GOAL:
  - Identification of critical operating parameters & operating ranges
  - Establishing “process robustness” especially multifactorial processes
  - A ROBUSTNESS STUDY provides assurance that the process will not fail within the defined process control limits
- Understand the process
- Determine process optimum
- Aid in assuring process operating limits
- Determine capability of a process step (e.g., to remove an impurity, clear a virus)
- Provides post-approval benefits (e.g., changes, deviations)

Development Studies (Identify)

- Scaled-down model (i.e,. laboratory scale) to assess process
  - Designed to be representative of the process unit operation and scale submitted for approval
- Scientific approximation of the commercial scale manufacturing process
  - Confidence in study and utility of results depends on qualification and conduct of the study
  - Qualified – quantitative, qualitative demonstration

Development Studies

- Design of Experiments
  - Factorial and response surface designs are useful in process definition, development, and validation
    - *Fractional factorials* efficiently test many variables
    - *Response surfaces* give precise info on critical variables
- Provides scientific, statistical assurance of process that cannot be achieved at commercial manufacturing scale

Development Studies

- Considerations
  - Model Qualification
    - How representative of commercial scale?
    - Address differences and their significance
  - Design & Conduct of Study
    - **Review of studies/ summary report**
      - Basis for protocol development
      - Review by process development scientists, process validation group, quality?

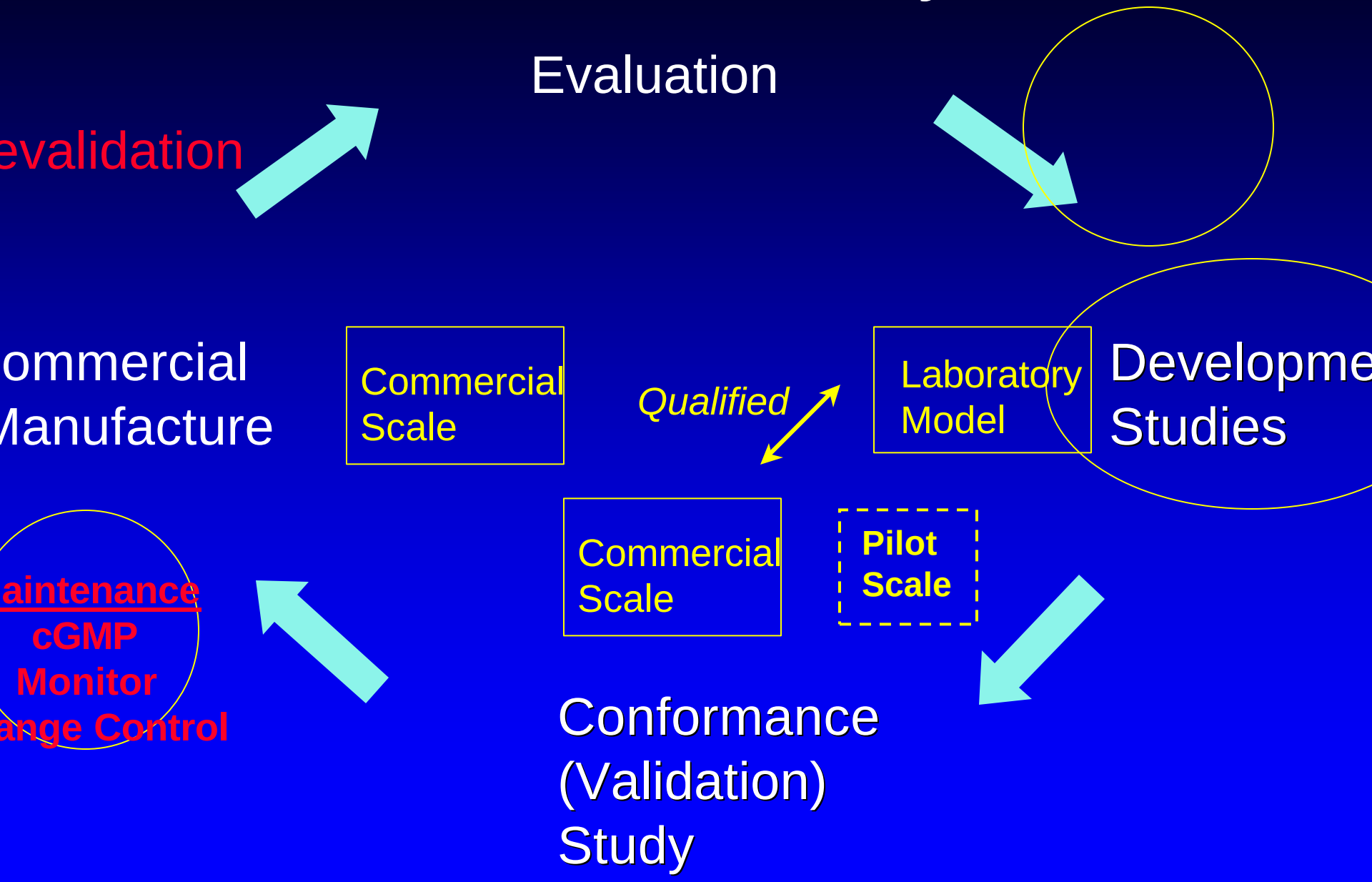
Conformance (Validation) Studies (Confirm)

- GOAL: Confirm that the process can function as intended - at commercial scale
- Production of Conformance Lots - Commercial scale (scale submitted for approval)
  - Operating parameters are controlled within limits
  - Specified intermediate and DS/ DP quality is achieved
  - Typically operated at set (target) values
- Transfer of information learned in development
- Confirmation truly occurs throughout the life-cycle (developmental, validation study, post approval)

Elements of a Conformance (Validation) Studies

- Validation Protocol
- Process Equipment
- Analytical Methods & Assays
- Summary Report

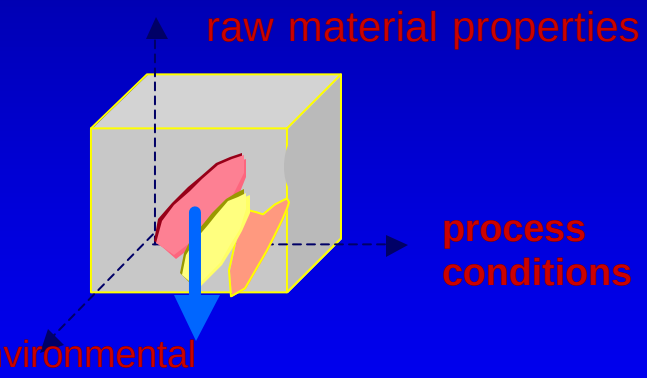
Validation Life Cycle



Conformance (Validation) Studies (Confirm)

- Considerations
  - Deficiency in IQ, OQ, systems, analytical ?
  - Sufficient data available
    - There are no data (inadequate data) to support …validation of ….
  - Demonstration of consistency (3 lots in sequence)
  - How realistically are these lots manufactured - how representative of commercial production?
  - Data substantiating that model is representative of and operated in a manner equivalent to the commercial scale process (e.g., virus and impurity removal)

Design Space



- Established a Design Space - operating within will produce a product meeting designed quality attributes
- Factor that influence product quality - environmental factors, process conditions, component properties
- Identification and Mitigation of Risks

Commercial Manufacture (Monitor)

- GOAL: Maintain the Validated State
- Consistent and Diligent Application of CGMPs
- Monitoring and trending of critical operating and performance parameters
  - Statistical Process Control & Other Analysis
  - Corrective and Preventative Action (CAPA)
- Effective Change Control program
  - Appropriate change control plan and procedures
  - Periodic reassessment of licensed process in light of current knowledge beyond routine change control
- Effective and Robust Quality Unit

Commercial Manufacture (Monitor)

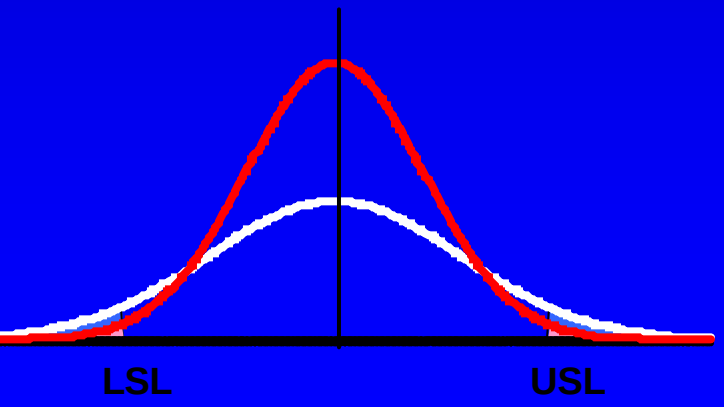
- Considerations
- Sources of variability not identified during development and validation
  - New component lot – important characteristic not identified
  - Critical variable not identified or limits inappropriate
- Ineffective Quality Oversight

Process Capability

- Process capability (normal manufacturing variation) accumulates with additional manufacturing
  - Due to variation in components, process, environment, etc.
  - Estimated and controlled for critical sources of variability in development
    - **Process validation studies (e.g., DOE), pilot scale, limited commercial production, evaluation of components**
- Confidence in achieving desired product quality accumulates with
  - Each lot manufactured
  - New lots of component, operating at different operating parameter ranges, different environmental conditions, etc.

Process Capability

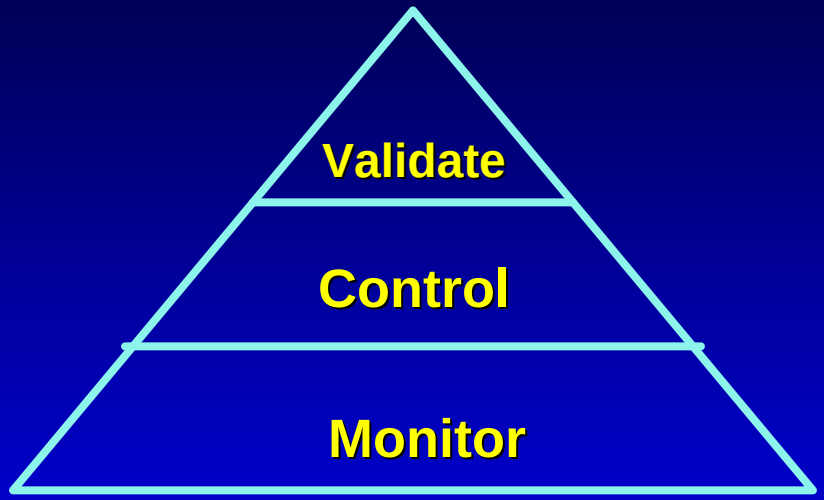
- With increased knowledge and experience of commercial manufacturing process, process variability should decrease or remain at existing level (as seen in clinical trial experience).
- Risk to quality is reduced by stable and capable manufacturing processes
- Improvement in Quality is a reduction of variability



Lower variability yields lower risk

What Gets Validated?

- What do I Validate ?
- What do I Control ?
- What do I Monitor ?

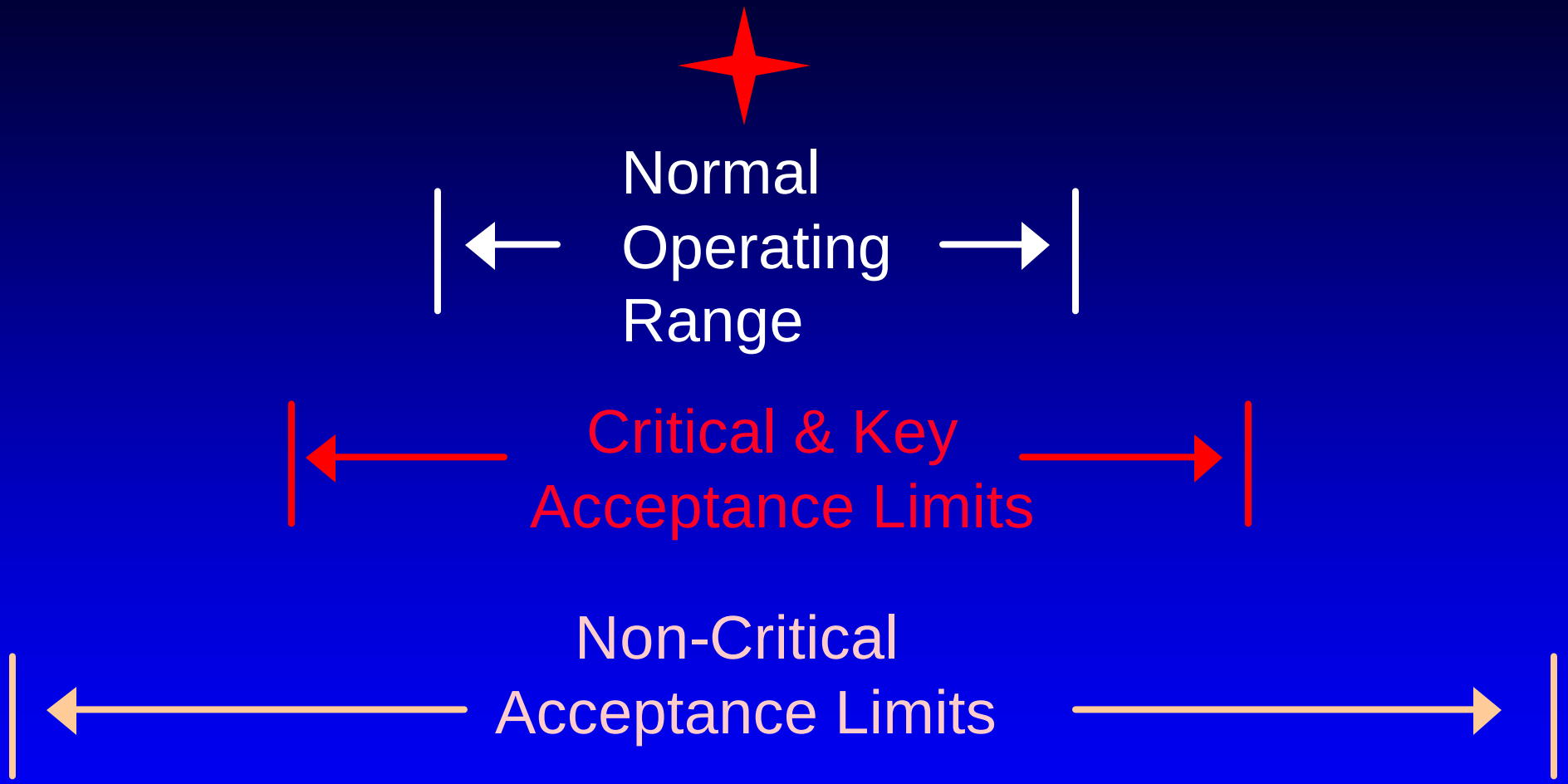


- What is Critical?
- Critical "A process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification". [ICH Q7A]

What is A Critical Operating Parameter

- Industry Proposal
  - **Critical operating variables - indicator of product quality**
  - **Non-critical operating variables - indicator of process performance**
  - **For non-critical operating variables, how close the variable has to be maintained within a known range determines if it is key or non-key**
- Important that the manufacturer and regulator knows;
  - **What variables were considered, what impacts the process, what variables affect the product (intermediate) quality, or do not**
  - **How variables are controlled, monitored or neither including how suitable acceptance criteria/ limits were determined as applicable**

Target/ Set Point



Process Analytical Technologies (PAT)

- *PAT* is a
  - **System** for designing, analyzing, and controlling manufacturing
  - Through timely measurements (i.e., during processing) of
  - Critical quality and performance attributes of
  - Raw and in-process materials and processes
- Goal
  - enhance understanding and control of drug quality system
  - supporting innovation and efficiency
- Development and implementation is voluntary

Process Validation and PAT

- Both PV (Life cycle) and PAT
  - Require process and product knowledge and understanding, creation of a design space (e.g., DOE studies)
  - Provide basis for process improvement
- With regard to process validation, PAT could
  - Continual monitoring of product quality attribute, process variable, (surrogate)
  - Increase product knowledge - faster rate - post-approval
  - Control Monitoring - Evaluating - Adjusting
  - Potentially reduces reliance on some elements of validation conformance batches
  - Continuous "verification" "continual validation"
- Currently, several challenges to achieve this with biotechnology/ biological products

Risk-based Regulatory Oversight

Risk Assessment - The capability of process control strategies to prevent or mitigate risk

Type of Product - Complexity, Intended Use, manufacturi complexity``

Products that serve a critical medical need, critical public health impact

Manufacturing operations critical to safety of product

The understanding of how manufacturing process factors affect product quality and performance

Effective Quality System

Compliance history, compliance status

Summary

- Demonstrating control of manufacturing process and validating a manufacturing process is a regulatory requirement.
- Understanding the product and the manufacturing process remains integral to the development and manufacture of biological and biotechnology products -“Know thy process and thy product”
- A comprehensive lifecycle approach to process validation relies on scientific & engineering principles, and progressively builds assurance (confidence) in consistent manufacture of quality product.

Summary

- Process validation impacts the product throughout its life-cycle and has potential benefits (e.g., deviations, process improvements)
- PV and PAT share several basis elements. Some elements of PAT could provide an enhanced assurance of product quality, and could result in modifications to process validation as currently performed

Summary

- FDA will continue to partner with manufacturers of existing and new products to facilitate implementing new technology and concepts, including those that can enhance knowledge, control and facilitate continuous improvement.

Acknowledgements

- Barry Cherney
- Mary Malarkey